REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 1-9 and 29-50 are pending and under consideration in the application. Claims 1-9, 29-41 and 44-50 stand rejected. Claim 42 has been indicated as allowable.

By the present amendment, claims 1-4, 6-8, 30, 34, 35, 39, 43 and 47 have been amended. Claim 1 has been amended to recite "comprising a nucleotide sequence". This is supported at least by as-filed claim 1. Claims 3 and 7 have been amended to recite a definite article, thereby restating the antecedent relationship of the vectors recited therein. Claims 4 and 8 have been amended to more extensively state the antecedent relationships of the polypeptides recited therein. Claim 35 has been amended to delete recitation of a functional characterization of the cell, and to depend from claim 34. Claim 36 has been amended to replace language describing the polypeptide recited therein with language from claim 33, from which claim 36 depend. Claims 2, 6, 30, 34, 39, 43 and 47 have been amended to repeat the adjective "isolated," which is recited in the independent claims from which they depend. Support for the amendments to claims 1-4, 6-8, 30, 34, 35, 39, 43 and 47 can be found throughout the specification and claims as originally filed, at least as previously described.

No prohibited new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on any subject matter that may have been canceled by way of this Amendment.

1. **Interview Summary**

An Interview Summary was mailed May 13, 2003, which was prepared by the Examiner without review by Applicants' representative. The Summary has been alleged to describe the substance of an interview conducted on April 16, 2003 between Applicants' representatives and the Examiner. Applicants agree with the portion of the Summary that indicates that the claims of record and the related art of record were discussed, and that it was agreed that the former rejection of claims 5, 9, and 29 under 35 U.S.C. § 102 should be withdrawn. However, Applicants respectfully note that the Summary contains further statements regarding matters upon which agreement was not reached. These statements appear to represent positions of the Examiner upon reflecting on the interview. Applicants respectfully disagree with that part of the Summary that describes matters on which agreement was not reached. Moreover, characterizations presented in the Summary of Applicants' views on matters in which agreement was not reached do not fully and precisely capture the views held and expressed by Applicants. Applicants' position on these matters is presented in Applicants' papers, including as set forth below.

2. **Claim Objections**

Claims 2, 6, 30, 34, 35, 39, 43, and 47 are objected to for alleged informalities. It has been suggested that these claims should be amended to recite "isolated" as in "isolated nucleic acid." Applicants respectfully submit that as a consequence of the dependency of these claims on claims that are directed to "an isolated nucleic acid," the term "isolated" would have been construed to apply to the nucleic acids that find their antecedent basis in those claims. However, simply in order to expedite prosecution, claims 2, 6, 30, 34, 35, 39, 43, and 47 have been amended to repeat the adjective "isolated" from the independent claims from which the rejected claims depend.

Claim 35 has been objected to because of errors. Claim 35 has been amended to correct an error in its dependency. The objection is not applicable to claim 35 as amended.

In view of the foregoing, withdrawal of the claim objections is respectfully requested.

3. Rejections withdrawn

The rejections of claims 1-3, 5-7, 9, 29-31, 33-36, 38-40, 43-44, 47-48 and 50 under 35 U.S.C. §§ 101 and 112, first paragraph for alleged lack of utility have been withdrawn.

The rejection of claims 5, 9, 29 and 50 under 35 U.S.C. § 102 as allegedly anticipated by Blattner et al. or Oshima et al. has been withdrawn.

The rejection of claims 29, 33 and 37-38 under 35 U.S.C. § 112, first paragraph, enablement requirement, has been withdrawn.

These rejections being withdrawn, Applicants understand that the formerly alleged grounds for rejection that have been repeated in numbered paragraphs 5-8 of the Office Action mailed January 15, 2004 are also considered withdrawn, unless restated in the grounds alleged for new rejections presented in the instant Official Action.

4. Previous Rejections under 35 U.S.C. §§ 101 and 112, first paragraph maintained

The previous rejection of claims 4, 8, 32, 37, 41, 45 and 49 under 35 U.S.C. §§ 101 and 112, first paragraph as allegedly not supported by a specific, credible and substantial utility or a well established utility, and allegedly not being enabled, have been maintained. The rejections are, again, respectfully traversed.

The Examiner has alleged that no specific biological function for a polypeptide encoded by SEQ ID NO: 1394 is taught in the specification. However, the specification teaches one skilled in the art to identify the function of the polypeptides encoded by the sequences that are disclosed by consulting databases for homologous polypeptides of known

function. *See*, for example at pages 37-39 and 48-49. Table 2 of the specification exemplifies results of one such procedure. The Table 2 entry for SEQ ID NO: 1394 (Table 2, column 3) identifies a homology relationship (columns 7 and 8) with an *E. coli* (column 9) gene having locus tag b1135 (column 10) and the gene name ymfC (column 11). At least by 1998, the gene product of ymfC had been identified as a pseudouridine synthase homolog. *See*, citation to a personal communication by K. Rudd cited in Ofengand and Fournier, 1998, at page 1605 of Del Campo et al. (RNA, 7:1603-15, 2001).

The gene product of ymfC was clearly not hypothetical, despite the initial name "hypothetical protein" in its Swissprot entry. Thus, Table 2 identifies SEQ ID NO: 1394 as having a high probability of a homology match to a protein of known function. The probability of being a random match was determined to be $P=9.0x10^{-95}$ (column 8). Further, it was known in the art at the time that pseudouridine synthases could be identified by certain distinct motifs. This is shown by Koonin (*Nucleic Acids Research*, 24:2411-15, 1996) and the creation of a PROSITE signature pattern for psuedouridine synthase in 1995 (PROSITE entry PS01149). The sequence encoded by SEQ ID NO: 1394 has sequences corresponding to the published conserved motifs. Thus, knowledge was available that would have independently taught one skilled in the art that SEQ ID NO: 1394 encodes a pseudouridine synthase and that also would have confirmed the significance of the identification in Table 2.

Therefore, it is clear that SEQ ID NO: 1394 and its encoded protein, identified in the specification and independently identifiable as a pseudouridine synthase had a well established utility, at the very least, for the conversion of uridine in the 23S RNA to pseudouridine. This is a specific, non-trivial utility. And, this utility is in addition to all of the utilities asserted in the specification that have been discussed at length throughout the history of this prosecution. One skilled in the art would have appreciated (1) that a

pseudouridine synthase polypeptide could be used to manipulate the pseudouridine content of RNA, and (2) that the nucleotide sequence could be used to provide, modulate, or block, a pseudouridine synthase functionality in a cell. Moreover, that fragments of the polypeptide can be used to raise antibodies at least for the purpose of detecting the presence of *E. cloacae* or the presence of this *E. cloacae* pseudouridine synthase and/or purifying pseudouridine synthase protein.

Applicants respectfully submit that these reasons are sufficient to show that all the requirements of 35 U.S.C. §§ 101 and 112, first paragraph, of a specific, substantial, and credible utility are satisfied for all of the currently submitted claims, including claims 4, 8, 32, 37, 41, 45, and 49. Furthermore, taken together with all the reasons previously discussed at length during the examination of this application, such as the number of specific substantial and credible utilities set forth in the specification. Applicants respectfully submit that the requirements of 35 U.S.C. §§ 101 and 112, first paragraph, are overwhelmingly satisfied. Withdrawal of the rejection of claims 4, 8, 32, 37, 41, 45, and 49 under 35 U.S.C. §§ 101 and 112, first paragraph, is again respectfully requested.

5. New Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 1-9, 29-41, 44-50 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The rejection is respectfully traversed. The standard for the written description requirement is described in M.P.E.P. § 2136. In relevant part, the test is described as follows:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such

> descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including . . . the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)(one must define a compound by "whatever characteristics sufficiently distinguish it"). M.P.E.P. § 2163(I).

Claims 1-4 have been rejected for issues alleged to arise from the recitation of "encoding an *E. cloacae* polypeptide" and "comprises SEQ ID NO: 1394." It has been alleged that SEQ ID NO: 1394 does not encode an *E. cloacae* polypeptide, because the first codon of SEQ ID NO: 1394 is not "AUG." However, as clearly explained in the specification at least at pages 31-32 and at page 38, the ORF's disclosed in this application are reported from a first codon following a preceding stop codon to the next stop codon in the *E. cloacae* genome. The specification teaches that "it will be recognized by one skilled in the art that the natural translation initiation sites will correspond to ATG, GTG or TTG" at page 38, lines 6-8. Accordingly, in the usage of the present specification, *E. cloacae* polypeptides encoded by sequences disclosed in the specification include polypeptides encoded within the disclosed ORFs beginning from a start codon identifiable therein. SEQ ID NO: 1394 has start codons at nucleotides 7, 16, and 37. *See*, page 31 at lines 19-26. SEQ ID NO: 1394 contains start and stop codons. Therefore, by definition, SEQ ID NO: 1394 encodes an *E. cloacae* polypeptide.

It has also been alleged that Applicants have not described or disclosed the "operon" which encodes the gene. It has also been suggested that the recitation of "comprising" in the claim includes regulatory sequences which are essential to the operation and function of the

structural gene in the operon. Applicants respectfully submit that no such requirement is implied by the recitation of "comprising" in claim 1. Claim 1, as amended, recites: "An isolated nucleic acid comprising a nucleotide sequence encoding an *E. cloacae* polypeptide wherein the nucleic acid comprises SEQ ID NO: 1394." Claim 1 does not recite or require a "gene" or an "operon." Claim 1 is directed to an isolated nucleic acid that encodes an *E. cloacae* polypeptide, i.e. an isolated nucleic acid that comprises a coding sequence of an *E. cloacae* polypeptide. Moreover, one skilled in the art at the time the application was filed was capable of either or both identifying native regulatory elements or recombinantly linking an exogenous transcription regulatory element to an isolated nucleic acid of claim 1 to make the vector recited in claim 2. The Official Action does not suggest, and certainly does not show, that making and using recombinant expression vectors for a given sequence encoding a polypeptide and choosing and linking any required elements for expression were not conventional in the art, or are not described in the specification.

Claims 5-8 have been rejected for the alleged reasons discussed above and a further alleged issue set forth as "written description support for a genus of nucleic acids that encode an *E. cloacae* polypeptide, of no specific biological function, of no specified size, and must only share 25 consecutive nucleic acids of SEQ ID NO: 1394." The rejection appears to be based on an allegation that the function of an *E. cloacae* polypeptide is insufficiently described, or that the polypeptide encoded by 25 consecutive nucleic acids of SEQ ID NO: 1394 may be too short to retain the function. Applicants respectfully submit that the function of the polypeptide encoded by SEQ ID NO: 1394 is identified in the specification and that conserved motifs of such polypeptides were know at the time the application was filed, as discussed above and previously. Moreover, Applicants further submit that the sufficiency, or alleged lack, of description of the function of any polypeptide encoded by the claimed nucleic

acid comprising 25 consecutive nucleic acids of SEQ ID NO: 1394 is irrelevant to the issue of the written description required to support claims 5-8, because no functional limitation is recited or implied in the claims.

Claim 5, and claims 6-8 that depend from claim 5, recite precise parameters that distinguish the clamed genus by defining the essential structural features, including a minimum size and a sequence element defined by reference to the disclosure of SEQ ID NO: 1394.

It has been suggested that claim 9 is not supported by a written description sufficient to satisfy the requirements of 35 U.S.C. § 112, first paragraph, because the sequence of claim 9 is not required to encode a polypeptide. Claim 9 recites a probe comprising a nucleotide sequence including at least 25 sequential nucleotides of SEQ ID NO: 1304. Whether or not claim 9 encodes a polypeptide is not directly related to its being a probe. Therefore, the stated issue is irrelevant to the written description support for claim 9.

As described in the specification at least at page 20 and pages 34-35, a probe can comprise a nucleic acid that specifically binds to a molecule of interest. Probes are often associated with or capable of associating with a label. The rejection does not suggest, and certainly fails to show, that labels for use in probes, or probe elements that provide for association with labels, were not conventional in the art at the time the application was filed. Claim 9 recites precise parameters defining the essential structural features of the claimed genus by reference to the disclosure of SEQ ID NO: 1394 so that the subject matter of claim 9 is fully supported by the specification.

With reference to claims 29-32, it is alleged that no *E. cloacae* polypeptides that comprise SEQ ID NO: 7056 are found to evidence original descriptive support. However, the specification as originally filed discloses SEQ ID NOS: 1394 and 7056, which describe an *E.*

cloacae derived nucleic acid and polypeptide respectively by definition in the specification. The specification states that:

> An '*E. cloacae*-derived' nucleic acid or polypeptide sequence may or may not be present in other bacterial species and may or may not be present in all *E. cloacae* strains. This term is intended to refer to the source from which the sequence was originally isolated. Specification at page 20, lines 12-15.

and

> This invention encompasses isolated *E. cloacae* polypeptides encoded by the disclosed *E. cloacae* genomic sequences, including the polypeptides of the invention contained in the Sequence Listing. Specification at page 50, lines 21-23.

SEQ ID NO: 1394 is disclosed as isolated from *E. cloacae* and as encoding SEQ ID NO: 7056. Thus, by definition, SEQ ID NO: 1394 is a nucleic acid within the scope of claims 29-32. Additional members of the claimed genus can be derived by reference to the conventional genetic code, which was in basic textbooks in the art at the time the application was filed. The Office Action makes allegations regarding the sufficiency of the disclosure concerning the function of the encoded polypeptide. As the claim does not recite or imply any functional limitation for the polypeptide, Applicants respectfully submit that the sufficiency, or alleged lack, of description of the function of any polypeptide encoded by the claimed nucleic acid is irrelevant to the written description required to support claims 29-32.

Claims 37-41 recite isolated nucleic acids encoding polypeptides that comprise at least 90% or 95% sequence identity with SEQ ID NO: 7056. It is alleged that Applicants have failed to show possession of the claimed invention. However, the specification as originally filed discloses SEQ ID NO: 7056, describes polypeptides having at least 90 or 95% identity to SEQ ID NO: 7056. *See*, for example, specification at page 10, lines 4-9. Identity is an unambiguous mathematical limitation, so that every polypeptide sequence meeting the

requirement of having at least 90% or 95% sequence identity with SEQ ID NO: 7056 can be logically determined.

It is also generally alleged that the written description of the present specification "does not provide for 'comprising language.' " The term "comprising" has a long and well established application in patent claims. "Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 U.S.P.Q.2d 1608, 1613 (Fed. Cir. 1997) (citing *In re Baxter*, 656 F.2d 679, 686, 210 U.S.P.Q. 795, 802 (C.C.P.A. 1981)). The transitional phrase, "comprising," is used in the present claims in accordance with well established practice. Essential elements, sufficient to distinguish the claimed invention are recited in the claims. The specification provides ample description of exemplary optional or preferred elements that may be added to the claimed nucleic acids and polypeptide sequences and still form constructs within the scope of the invention. Disclosure of SEQ ID NO: 1394, together with description throughout the specification provides adequate written description of the claimed invention in view of the knowledge in the art at the time the application was filed.

The analysis of Example 8 of the Revised Interim Written Description Guidelines Training Materials illustrates the stated position of the U.S.P.T.O. regarding claims using open language, with the example claim similar to claims 1, 29, and 33. One of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 1394, because e.g. SEQ ID NO: 1394 can be readily embedded in known vectors. Although there may be substantial variability among the species of DNAs encompassed within the scope of the claim, because SEQ ID NO: 1394 may be combined with sequences known in the art, e.g. expression vectors, the necessary common attribute is the open reading frame (ORF) (SEQ

ID NO: 1394). Weighing all factors including (1) that the full length ORF (SEQ ID NO: 1394) is disclosed, and (2) that any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that Applicants were in possession of the genus of DNAs that comprise SEQ ID NO: 1394. Example 8 concludes that in the case of an open language claim reciting a sequence comprising a complete ORF, the written description requirement is satisfied.

Similarly, claims 5, 9, and 50 each describe a genus of molecules comprising a fragment of SEQ ID NO: 1394. A large and representative number of species within each genus can be directly derived by systematically listing fragments of SEQ ID NO: 1394 having at least the recited number of sequential nucleotides. Each of these claims is described by reference to a full length ORF. Thus, the essential structural feature of every member of the genus can be determined by reference to the full length ORF and any substantial variability within the genus beyond the directly derivable species arises due to addition of elements that are not particular to the presently claimed invention. Accordingly, the use of open language with respect to the claimed nucleic acids is clearly acceptable under the U.S.P.T.O. interpretation of the written description requirement as exemplified in the Revised Interim Written Description Guidelines Training Materials.

5.1 ***New Matter Rejection***

Claims 33-36 and 46-49 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. The rejection is respectfully traversed.

Claim 33 recites an isolated nucleic acid which encodes a polypeptide of *E. cloacae* consisting of a range of residues which is 3-222, 6-222, or 13-222 of SEQ ID NO: 7056. Claims 34-36 depend from claim 33. Claim 46 recites an isolated nucleic acid consisting of nucleotides 7-669, 16-669, or 37-669 of SEQ ID NO: 1394. Claims 47-49 depend from claim 46.

It has been alleged that no specific guidance to select the recited ranges of encoded amino acids could be found to evidence original descriptive support in the specification. It is well established that *in haec verba* description is not required. See, e.g., M.P.E.P. § 2163. Thus, even if the recited ranges are not disclosed *in haec verba*, the written description requirement is satisfied if there are "blazemarks" in the specification that would have led one of ordinary skill to the claimed invention. *See, Purdue Pharma L.P. v. Faulding Inc.*, 56 U.S.P.Q.2d 1481, 1486 (Fed. Cir. 2000).

The Examiner's attention is respectfully directed to the specification at pages 31-32 and 38. At page 31, it is explained that the nucleic acid sequences disclosed in the Sequence Listing are "based on stop-to-stop codon reads." It is further disclosed that these "ORFs may contain start codons which indicate the initiation or protein synthesis of a naturally-occurring *E. cloacae* polypeptide." The specification teaches that it "will be recognized by one skilled in the art that the natural translation initiation sites will correspond to ATG, GTG or TTG codons" at page 38. Thus one skilled in the art would recognize that SEQ ID NO: 1394 has start codons such as disclosed in the specification beginning at nucleotides 7, 16, and 37 corresponding to residues 3, 6, and 13 of SEQ ID NO: 7056. From at least the foregoing, it is clear that there are specific blazemarks in the specification that would direct one skilled in the art to select the recited ranges. *See, Purdue Pharma L.P. v. Faulding Inc.*, at 1486.

Therefore, Applicants respectfully submit that the subject matter of claims 33-36 and 46-49 is not prohibited new matter.

For at least the above reasons, the rejections of claims under 35 U.S.C. § 112, first paragraph, the written description requirement, are respectfully traversed and withdrawal of the rejections is respectfully requested.

6. New Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-9, 29-41, and 43-50 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not enable any person skilled in the art to make and/or use the invention commensurate in scope with these claims. The rejection is respectfully traversed.

The rejection is allegedly based on an analysis of factors set forth *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*, 230 USPQ 546 (BdPatApp&Int 1986). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Wands*, at 1404.

However, the rejection does not establish a *prima facie* case of obviousness on full application of the *Wands* factors to the instant specification and the rejected claims. For example, the rejected claims have not been properly construed as required by *Wands* and M.P.E.P. § 2164.04. Under the *Wands* factor heading "breadth of the claims," the only assertion in support of the rejection is the word "broad." The scope of each of the rejected claims is different. Some of the rejected claims are directed to nucleic acids or probes, some are directed to expression vectors and others to cells and methods of expressing a

polypeptide. The scope of the nucleic acid element differs between sets of claims. Some of the rejected claims recite sequences including complete coding sequences while others recite fragments of the disclosed sequence. Some of the rejected claims recite minimum amounts of sequence identity, while other claims do not recite variations in the sequence. A rejection for an alleged lack of enablement for the scope of the claims can only be established in terms of the scope of each individual claim.

The rejection has not been presented with respect to the scope of the particular rejected claims. Applicants' respectfully submit that scope of each of the rejected claims is commensurate with the guidance provided in the specification and the considerable skill in the art.

Under the *Wands* factor heading "quantity of experimentation," allegations have been made with regard to certain aspects of a limited number of possible uses of the claimed nucleic acids. However, the specification discloses how to use the claimed nucleic acids in a wide variety of applications, and one skilled in the art would be aware of additional uses for the claimed nucleic acids. The correspondence between the scope of each claim and the enablement provided by the specification taken with the knowledge available to one skilled in the art must be considered with regard to all of the various disclosed and known uses. M.P.E.P. § 2164.01(c) states that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention."

The rejection does not evidence consideration of all of the various uses disclosed in the application or known to one of skill in the art. To support a *prima facie* case of lack of enablement, the rejection must show a reason to believe that the claimed invention is not enabled for any use without undue experimentation. Absent such a showing, the rejection cannot support a *prima facie* case of non-enablement.

Moreover, the quantum of experimentation that would be considered unreasonable for any of the uses disclosed in thee specification or known in the art has not been addressed. Enablement is not precluded by the necessity for some experimentation, such as routine screening. Experimentation needed to practice the invention must not be undue experimentation. "the key word is 'undue,' not 'experimentation.' " *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Id.* (citing *Ansul Co. v. Uniroyal, Inc.*, 169 USPQ 759, 762-63 (2d Cir. 1971)). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

The rejection fails to establish a standard of reasonable experimentation for each of the various applications of the claimed nucleic acids, probes, vector, cells, and methods. Any amount of experimentation required to practice the several applications that are disclosed in the specification and/or known to one skilled in the art varies with each application. Applicants submit that in every case, any required experimentation would have been considered reasonable by practitioners in the art.

The bare allegations of the present rejection do not establish that any quantity of experimentation implicated by the allegations would be considered undue by persons of ordinary skill. Therefore, the rejection fails to establish a *prima facie* case that any experimentation required to practice the present invention is undue. Let alone that the application is not enabled.

Further, allegations under the *Wands* factor heading "quantity of experimentation" have little relevance to the question of enablement. For example, it has been alleged that "nucleic acids that encode therapeutic polypeptides is unpredictable in the art." This is repeated under the heading "the predictability or unpredictability of the art." However, no limitation or requirement that polypeptides encoded by the claimed nucleic acid sequence be therapeutic is recited, or may be implied, in the rejected claims, and none of the claims is limited to vaccines. For example, claims 9 and 50 are directed to probes. Moreover, numerous uses for the claimed nucleic acids and/or the polypeptides that they can encode are described in the specification that do not implicate any therapeutic function, or even require the native biological function. For example, raising antibodies for use as clinical and research reagents, as bait in a two-hybrid screen, as targets in screening assays, and other uses for the polypeptides are disclosed. Further uses for the nucleic acid sequences are also disclosed that do not require that any functional polypeptide be encoded.

It is also alleged that the nucleic acid is an incomplete open reading frame (ORF) that does not start with "Met." However, the sequence is not an incomplete reading frame. The Examiner's attention is directed to pages 31-32 and 38 of the specification as discussed above. Moreover, one skilled in the art is more than capable of providing a start codon when expression of a polypeptide fragment from a nucleic acid sequence that does not start with ATG is desired.

It has also been alleged that "Del Campo et al. teaches knock-out mutants of [pseudouridine synthase] but the knock-out strains grew just as well as the wild-type strains, thus defining a non-essential gene, that would not serve as a target for a therapeutic target." It is true that four pseudouridine synthase knock-out *E. coli* strains created by Del Campo et al. showed no difference in exponential growth. However, Offengard (the corresponding

author of the Del Campo et al. paper) and coworkers also reported that even when no difference in exponential growth rates were observed, deletion of a pseudouridine synthase inflicted a selective disadvantage in *E. coli*. *See*, Gutsell et al. RNA 6:1870-81 (2000) and Raychaudhuri et al., J. Biol. Chem., 274:1880-86 (1999). Offengard and coworkers stated that since the defect was not observed in the exponential phase, the next most likely conclusion was that the defect affected the stationary phase of the bacterial cell cycle. Further, Offengard and coworkers also reported pseudouridine synthases shown to be essential. *See,* Raychaudhuri et al., RNA 4:1407-17 (1998). Further, it was understood in the art that pseudouridine synthases were essential before the present application was filed. *See*, Koonin, Nucleic Acids Research, 24:2411-15 (1996). Taking all the evidence together, the allegation does not establish that the application is not enabling for the use of claimed sequences in a screening method for therapeutic agents. Even if it did, the finding could not lead to a conclusion that the claimed invention is not enabled, because many other applications are taught in the specification or would have been recognized by one skilled in the art.

Under the heading "amount of direction or guidance presented", it is alleged that none is provided. Plainly, the amount of guidance is not "none" as alleged. In fact, the specification provides extensive guidance concerning how to make and use the nucleic acids of the invention. For example, the specification provides guidance with respect to making and using probes at pages 21-22, making analogs and conservative substitutions at pages 24-25, how to use nucleic acid sequences as a capture ligand at page 35, how to make and use antisense nucleic acids at pages 36, 37, expression of polypeptides at pages 40-42, making and using a library comprising the disclosed sequences at page 42, making and using antibodies reactive to peptides of the invention at pages 75-78, how to use polypeptides

encoded by the claimed nucleic acids for drug screening at pages 80-81, how to perform an over-expression assay using the claimed invention at pages 81-82, and more. The specification provides substantial guidance with respect to how to make and use the claimed nucleic acids, and polypeptides that can be encoded by the claimed nucleic acids.

Under the headings "state of the prior art" and "the relative skill of those in the art," it has been acknowledged that both the knowledge and skill in the art were high. There were no prior identified *E. cloacae* pseudouridine synthases. However, signature motifs of pseudouridine synthases were known so that the claimed sequence could be identified as an essential enzyme and conserved residues, which one skilled in the art would have understood as likely to be more or less essential, could be recognized. *See, e.g.,* Koonin, Nucleic Acids Research, 24:2411-2415 (1996). One skilled in the art would have had considerable knowledge of how to make and use a nucleic acid sequence that had been identified as encoding an essential enzyme of a particular pathogen, so that one skilled in the art would know how to make and use the claimed invention once provided with the disclosure of the sequence, together with the ample guidance of the specification.

In view of the foregoing, Applicants respectfully submit that the rejection has not set forth a *prima facie* case that the rejected claims are not enabled by the specification. Rather, in view of the considerable guidance of the specification taken with the knowledge of one skilled in the art, consideration of the *Wands* factors actually supports a conclusion that the claims are fully enabled. Accordingly, withdrawal of the rejection is respectfully requested.

7. **New Rejections under 35 U.S.C. § 112, second paragraph**

Claims 1, 3-5, 7, 8, 35, and 36 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

Claim 1 has been rejected for reciting "an isolated nucleic acid encoding an E. cloacae polypeptide wherein the nucleic acid comprises SEQ ID NO:1394," because allegedly no *E. cloacae* polypeptides have been described or defined that are encoded by a nucleic acid that comprises SEQ ID NO: 1394. As described throughout the specification, SEQ ID NO: 1394 is an open reading frame (ORF) of the *E. cloacae* genome comprising start and stop codons. *See*, for example pages 31-32 and 38. By definition in the specification SEQ ID NO: 1394 encodes an *E. cloacae* polypeptide. Thus, claim 1 is not indefinite. However, simply in order to expedite prosecution, claim 1 has been rewritten to more nearly reflect the language of claim 1, as originally presented. The metes and bounds of claim 1 are clearly defined. Claim 1, as amended, clearly satisfies the requirements of 35 U.S.C. § 112, second paragraph.

Claims 3 and 7 have been rejected because the antecedent basis of the vectors recited therein is allegedly unclear. Applicant respectfully submits that one of skill in the art would understand that "a recombinant expression vector of claim 2" clearly meant the recombinant expression vector of claim 2. Nevertheless, simply to expedite prosecution of the application, claims 3 and 7 have been amended to recite a definite article. Claims 3 and 7, as amended, clearly convey the antecedent relationships of the vectors recited therein.

Claims 4 and 8 have been rejected, because it is allegedly unclear what polypeptide is being produced by the recited methods. Claim 4 depends from claim 3, which depends from claim 2, which depends from claim 1. Claim 8 depends from claim 7, which depends from claim 6, which depends from claim 5. Therefore claim 4 incorporates all the elements of

claims 3, 2, and 1. Likewise, claim 8 incorporates all the elements of claims 7, 6, and 5. Thus, it would be understood that "the polypeptide" recited in claim 4, has antecedent basis in the *E. cloacae* polypeptide of claim 1 that is encoded on the isolated nucleic acid in the vector in the cell recited in claim 4; and, similarly the polypeptide recited in claim 8 has antecedent basis in claim 5. Nevertheless, simply in order to expedite prosecution, claims 4 and 8 have been amended to more profusely point out that the polypeptide encoded on the isolated nucleic acid of claim 1 in the method of claim 4, and the polypeptide encoded by the isolated nucleic acid of claim 1 is expressed in the method of claim 8.

Claim 5 has been rejected, allegedly because "claim 5 recites the phrase 'An isolated nucleic acid encoded an E cloacae polypeptide', 'wherein the nucleic acid comprises at least 25 sequential bases of SEQ ID NO: 1394.'" This statement leaves out a portion of claim 5 and suggests that the Examiner has neglected to consider claim 5 as a whole. In fact, claim 5 recites "An isolated nucleic acid encoding an *E. cloacae* polypeptide *or a fragment thereof*, wherein the nucleic acid comprises at least 25 sequential bases of SEQ ID NO: 1394." [italics added] The recitation of an isolated nucleic acid encoding an *E. cloacae* polypeptide *or a fragment thereof* is not in conflict with the recitation that the nucleic acid comprises at least 25 sequential bases of SEQ ID NO: 1394. The rejection alleges that 25 sequential bases of SEQ ID NO: 1394 would encode about 8 amino acids, and that "a sequence of 8 amino acids [is not] unique to *E. cloacae* at the polypeptide level." Applicants respectfully submit that this is irrelevant to the issue of whether the claim satisfies 35 U.S.C. § 112, second paragraph. As framed, this rejection appears to relate more to the question of patentability under 35 U.S.C. § 102, but no reference that anticipates claim 5 has been made of record. Claim 5, considered as a whole, is clear and definite.

Claims 4, 8, 32, 36, 41, 45, and 49 are rejected under 35 U.S.C. § 112, second paragraph as allegedly incomplete. Claims 4, 8, 32, 36, 41, 45, and 49 describe methods of producing *E. cloacae* polypeptides comprising culturing cells containing recombinant expression vectors encoding the polypeptides under conditions that permit expression of the polypeptide. In alleging that the rejected claims are incomplete, the Examiner asks "How does the step of culturing correlate with the intended use of producing the polypeptide? Doesn't production of the polypeptide require expressing and isolating the polypeptide?" Applicants respectfully submit that "expressing" a polypeptide is a function of the cell, not a step that a person takes; although, it is understood that the term expressing is sometimes used in the art as shorthand for culturing a cell comprising a recombinant expression vector under conditions that permit the expression of a polypeptide encoded on the vector. Thus, the recited step of culturing a cell comprising a recombinant expression vector comprising an isolated nucleic acid sequence operably linked to a transcription regulatory element and encoding a polypeptide under conditions that permit expression of the polypeptide is sufficient to accomplish the purpose of producing the polypeptide. How to perform the culturing step is described in the specification and would have been well known to the skilled practitioner in the art at the time the application was filed. Further, as the claims do not recite producing an isolated polypeptide, no isolation step is required; although, such steps are clearly optional within the scope of the open language of the rejected claims.

Claims 35 and 36 have been rejected for reciting language describing the polypeptides described therein that was allegedly inconsistent with language used in a parent claim. Claims 35 and 36 have been amended. Claim 35 has been amended to delete the unnecessary functional language that was objected to. Claim 36 was amended to replace the language that was objected to with language from a parent claim.

Claim 35 has been rejected for reciting a recombinant expression vector of claim 33, which does not recite a recombinant expression vector. Claim 35 has been amended to refer to claim 34, which recites a recombinant expression vector.

For at least the foregoing reasons, 1, 3-5, 7, 8, 35 and 36, as currently presented satisfy the requirements of 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection of these claims is respectfully requested.

8. New Rejections under 35 U.S.C. § 102(b)

Claims 3-4, 7-8, 31-32, 34-35, 40-41, 44-45 and 48-49 have been rejected under 35 U.S.C. § 103 as allegedly anticipated by Rattray et al., *Applied and Environmental Microbiology*, 61:2950-57 (1995). Rattray et al. describe an *E. cloacae* cell comprising a lux plasmid. The lux plasmid permits observation of the cells by luminence detection. The Examiner states that she is "reading the phrase 'cell comprising a recombinant expression vector' to include an E. cloacae cell that evidence[s] changes from the wild-type cell, but comprise[s] all of the genes that normally are present in an E. cloacae cell." Such a reading implies that any non-wild-type cell necessarily comprises a recombinant expression vector. This construction is not reasonable, because it is clearly not consistent with the usual meaning of "recombinant expression vector" in the art. But even if the Examiner's construction were reasonable, which it is not, it must be noted that the rejected claims do not encompass cells comprising any recombinant expression vector. The rejected claims recite specific recombinant expression vectors comprising specific isolated nucleic acid sequences. The term "isolated nucleic acid" is defined in the specification in such a manner as to exclude a naturally occurring genome, and the lux plasmid of Rattray et al. does not carry sequences that are included in the vectors of the presently claimed invention.

Rattray *et al.* do not suggest or describe the presently claimed invention. For example, claim 3 recites a cell comprising a recombinant expression vector of claim 26. (as amended, claim 3 recites "the" recombinant expression vector of claim 2.) A recombinant expression vector of claim 2 comprises the nucleic acid of claim 1 operably linked to a transcription regulatory element. The nucleic acid of claim 1 is an isolated nucleic acid comprising a nucleotide sequence encoding an *E. cloacae* polypeptide wherein the nucleic acid comprises SEQ ID NO: 1394. Rattray et al. do not teach or suggest an isolated nucleic acid comprising SEQ ID NO: 1394, a recombinant expression vector comprising such an isolated nucleic acid, a cell comprising such a recombinant expression vector, or a method of producing a polypeptide comprising culturing such a cell.

Rattray *et al.* fail to teach all the elements of any of claims 3-4, 7-8, 31-32, 34-35, 40-41, 44-45 and 48-49 arranged as in the claims. Accordingly, Rattray *et al.* does not anticipate claims 3-4, 7-8, 31-32, 34-35, 40-41, 44-45, and 48-49. *See, e.g.*, M.P.E.P. § 2131. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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